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09/889383

JC18 Rec'd PCT/PTO 1 7 JUL 2001

## TRANSMITTAL LETTER TO THE UNITED STATES

ATTORNEY'S DOCKET NUMBER 0480/01211

DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP 00/00306	15 January 2000	22 January 1999

TITLE OF INVENTION: A PROCESS FOR REDUCING THE CONTENT OF ETHYL 3-DIMETHYLAMINO-2-PHENYLPROPIONATE  
IN SOLUTIONS OF ETHYL 2-DIMETHYLAMINO-1-PHENYL-3-CYCLOHEXENE-1-CARBOXYLATE

APPLICANT(S) FOR DO/EO/US Marco THYES, Wolfgang FALKENBERG, Ulrich SCHNEIDER

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following  
items and other information:

1. /X/ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
  2. / / This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
  3. /X/ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
  4. /x/ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
  5. /X/ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
    - a. /X/ is transmitted herewith (required only if not transmitted by the International Bureau).
    - b. / / has been transmitted by the International Bureau.
    - c. / / is not required, as the application was filed in the United States Receiving Office (RO/USO).
  6. /X/ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
  7. / / Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
    - a. / / are transmitted herewith (required only if not transmitted by the International Bureau).
    - b. / / have been transmitted by the International Bureau.
    - c. / / have not been made; however, the time limit for making such amendments has NOT expired.
    - d. / / have not been made and will not be made.
  8. / / A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
  9. / / An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
  10. / / A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
- Items 11. to 16. below concern other document(s) or information included:
11. /X/ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
  12. / / An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
  13. /x/ A FIRST preliminary amendment.  
/ / A SECOND or SUBSEQUENT preliminary amendment.
  14. / / A substitute specification.
  15. / / A change of power of attorney and/or address letter.
  16. /x/ Other items or information.  
International Search Report  
International Preliminary Examination Report

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U.S. Appl. No. (If Known) INTERNATIONAL APPLN. NO.  
PCT/EP00/00306ATTORNEY'S DOCKET NO.  
0480/01211

	<u>CALCULATIONS</u>	<u>PTO USE ONLY</u>
17. /X/ The following fees are submitted		
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the		
EPO or JPO.....\$860.00	860.00	
International preliminary examination fee paid to USPTO		
(37 CFR 1.482).....\$750.00		
No international preliminary examination fee paid to		
USPTO (37 CFR 1.482) but international search fee paid		
to USPTO (37 CFR 1.445(a)(2)).....\$700.00		
Neither international preliminary examination fee		
(37 CFR 1.482) nor international search fee		
(37 CFR 1.445(a)(2)) paid to USPTO .....\$ 970.00		
International preliminary examination fee paid to		
USPTO (37 CFR 1.482) and all claims satisfied pro		
-visions of PCT Article 33(2)-(4).....\$96.00		

ENTER APPROPRIATE BASIC FEE AMOUNT = \$ 860.00

Surcharge of \$130.00 for furnishing the oath or declaration  
later than / / 20 / / 30 months from the earliest  
claimed priority date (37 CFR 1.492(e)).

<u>Claims</u>	<u>Number Filed</u>	<u>Number Extra</u>	<u>Rate</u>	
Total Claims	1	-20		X\$18.
Indep. Claims	1	-3		X\$80.
Multiple dependent claim(s) (if applicable)		+270.		

<b>TOTAL OF ABOVE CALCULATION</b>	=	860.00	
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Reduction of 1/2 for filing by small entity, if applicable.  
Verified Small Entity statement must also be filed  
(Note 37 CFR 1.9, 1.27, 1.28).

<b>SUBTOTAL</b>	=	860.00	
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Processing fee of \$130. for furnishing the English  
translation later than / / 20 / / 30 months from the  
earliest claimed priority date (37 CFR 1.492(f)).

<b>TOTAL NATIONAL FEE</b>	=	860.00	
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Fee for recording the enclosed assignment (37 CFR 1.21(h)).  
The assignment must be accompanied by an appropriate cover  
sheet (37 CFR 3.28, 3.31) \$40.00 per property

<b>TOTAL FEES ENCLOSED</b>	= \$	860.00	
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Amount to be

refunded: \$

Charged \$

a./X/ A check in the amount of \$ 860. to cover the above fees is enclosed.

b./ / Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \$ \_\_\_\_\_ to cover the above fees. A duplicate copy of this sheet is enclosed.

c./X/ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 11-0345. A duplicate copy of this sheet is enclosed.

**NOTE:** Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

KEIL &amp; WEINKAUF

1101 Connecticut Ave., N.W.

Washington, D. C. 20036

SIGNATURE

Herbert B. Keil

NAME

Registration No. 18,967

09/889383

JC18 Rec'd PCT/PTO 1 7 JUL 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of )  
THYES et al. ) BOX PCT  
)  
International Application )  
PCT/EP 00/00306 )  
)  
Filed: Jan 27, 2000 )  
January 15, 2000 )  
)

For: A PROCESS FOR REDUCING THE CONTENT OF ETHYL 3-DIMETHYLAMINO-2-PHENYLPROPIONATE IN SOLUTIONS OF ETHYL 2-DIMETHYLAMINO-1-PHENYL-3-CYCLOHEXENE-1-CARBOXYLATE

PRELIMINARY AMENDMENT

Honorable Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

Sir:

Prior to examination, kindly amend the above-identified application as follows:

IN THE CLAIMS

Kindly amend the claim as shown in the attached sheet.

REMARKS

The sole claim in the case has been amended to put the claim in better form for U.S. filing. No new matter is included.

Favorable action is solicited.

Respectfully submitted,

KEIL & WEINKAUF

*H B Keil*  
Herbert B. Keil  
Reg. No. 18,967

1101 Connecticut Ave., N.W.  
Washington, D.C. 20036

(202)659-0100

## CLEAN VERSION OF THE CLAIM - 0480/01211

A process for reducing the content of ethyl 3-dimethylamino-2-phenylpropionate in a solution, contaminated therewith, of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in a water-immiscible solvent, which comprises adding from 0.5 to 2.0 equivalents of a carboxylic acid per mole of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate to this solution, and stirring this mixture at a temperature of from 50°C to 100°C, wherein the content of 3-dimethylamino-phenyl-propionic acid-ethylester is below 0.10%.

## MARKED UP VERSION OF THE CLAIM - 0480/01211

A process for reducing the content of ethyl 3-dimethylamino-2-phenylpropionate in a solution, contaminated therewith, of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in a water-immiscible solvent, which comprises adding from 0.5 to 2.0 equivalents of a carboxylic acid per mole of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate to this solution, and stirring this mixture at a temperature of from 50°C to 100°C, wherein the content of 3-dimethylamino-phenyl- propionic acid-ethylester is below 0.10%.

A process for reducing the content of ethyl  
3-dimethylamino-2-phenylpropionate in solutions of ethyl  
2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate

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The invention relates to a process for reducing the content of  
ethyl 3-dimethylamino-2-phenylpropionate (2) in ethyl  
2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate (1), which  
is a starting material for preparing the analgesic tilidine.

10 Tilidine is the trans isomer of ethyl

2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate and is  
commercially available as tilidine hydrochloride hemihydrate.

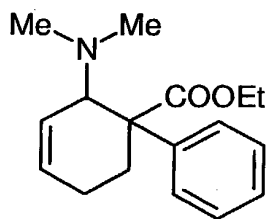
Ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate

- 15 results as a mixture of cis and trans isomers on reacting ethyl  
atropate with 1-dimethylaminobutadiene. DE 1 923 620 describes a  
process for preparing ethyl  
2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in which it  
is unnecessary to employ the 1-dimethylaminobutadiene in isolated  
20 form for reaction with ethyl atropate; on the contrary, the  
process entails reacting crotonaldehyde in the presence of  
potassium carbonate as water-binding agent and of catalytic  
amounts of a quinone in an inert solvent at from 3 to 5°C with  
dimethylamine, and reacting the product obtained in this reaction  
25 with ethyl atropate to give ethyl 2-dimethylamino-1-  
phenyl-3-cyclohexene-1-carboxylate (mixture of cis and trans  
isomers).

The synthesis is accompanied by the formation of a second

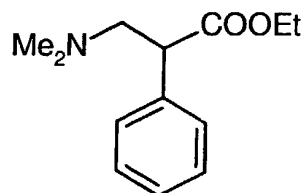
30 component, ethyl 3-dimethylamino-2-phenylpropionate.

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(1)

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(2)

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Ethyl 3-dimethylamino-2-phenylpropionate is produced in the reaction mixture formally by addition of dimethylamine onto ethyl atropate, the dimethylamine being liberated for example as a consequence of polycondensation of 1-dimethylaminobutadiene or as  
5 a consequence of processes of condensation between 1-dimethylaminobutadiene and excess crotonaldehyde.

The extent of the formation of ethyl 3-dimethylamino-2-phenylpropionate depends on the molar ratio of the amounts of ethyl atropate and dimethylamine reacted and is moreover influenced by the nature of the solvent employed [Ann. Chem. 728, 64 (1969)]. The presence of potassium carbonate during the reaction appears to inhibit the formation of ethyl 3-dimethylamino-2-phenylpropionate.

15 The ethyl 3-dimethylamino-2-phenylpropionate is not removed in the known way (DE 1.923.620) for isolating and purifying ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate (mixture of cis and trans isomers). In the separation of isomers in a known  
20 manner (DE 1 923 620, GB 1 226 318), e.g. by selective complex formation with zinc ions or selective salt formation with oxalic acid, which is necessary for isolating tilidine (trans isomer), there is in fact enrichment of the impurity relative to the active substance (DE 1 923 620), with the consequence that, in  
25 order to meet the specification of a maximum of 0.10% ethyl 3-dimethylamino-2-phenylpropionate in tilidine hydrochloride hemihydrate, removal must be carried out, for example by recrystallization of the tilidine salt.

30 It is admittedly stated in DE 1 923 620 that it is possible in principle on preparation of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate by the process described above to achieve an ethyl 3-dimethylamino-2-phenylpropionate content of about 0.1%.

35 However, it has emerged in practice that the content is from 0.3 to 2%.

It is an object of the present invention to provide a simple, low-cost process for reducing the ethyl 3-dimethylamino-2-phenylpropionate content at an early stage of tilidine preparation.

We have found that this object is achieved by a process for reducing the content of ethyl 3-dimethylamino-2-phenylpropionate 45 in a solution, contaminated therewith, of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in a water-immiscible solvent, which comprises adding from 0.5 to 2.0

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equivalents of a carboxylic acid per mole of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate to this solution, and stirring this mixture at a temperature of from 50°C to 100°C.

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Suitable water-immiscible solvents are aromatic hydrocarbons such as toluene, cyclic or acyclic aliphatic hydrocarbons, such as cyclohexane, or aliphatic ethers such as diisopropyl ether. Aromatic and aliphatic carboxylic acids such as formic acid and,

- 10 preferably, acetic acid are suitable as carboxylic acid. The acid is employed in an amount of from 0.5 to 2.0 equivalents, preferably 0.75 to 1.25 equivalents, per mole of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate.

- 15 The mixture obtained in this way is stirred at a temperature of from 50°C to 100°C, preferably 70°C to 90°C, until the ethyl 3-dimethylamino-2-phenylpropionate content reaches a level which can be tolerated for the subsequent preparation process, as a rule for about 0.5 to 2 hours.

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After the end of the reaction, the ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate is isolated from the reaction mixture in a conventional way. Thus, the ester can be isolated and purified by adding water to the reaction mixture and making it alkaline. The aqueous phase can then be separated off, and the organic phase can be washed where appropriate with sodium disulfite solution and concentrated.

- This results in an ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate which has an ethyl 3-dimethylamino-2-phenylpropionate content below 0.10%.

- It is preferred to use for the purification the mixture of cis and trans isomers which is produced initially in the synthesis of the ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate. Virtually no cis/trans isomerization of the ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate is observed on removal of ethyl 3-dimethylamino-2-phenylpropionate by the novel process. This contrasts with the setting up of an isomer equilibrium observed (DE 1 951 587) on heating ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in glacial acetic acid or aqueous acetic acid. Since virtually no cis/trans isomerization occurs in the novel purification process, it can also be applied in particular to tilidine itself, i.e. to the trans isomer of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate. It is, of course, also possible however for the ethyl



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2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate to be in the cis form for the purification.

The novel process is based formally on elimination of dimethylamine from ethyl 3-dimethylamino-2-phenylpropionate. The ethyl atropate formed by the elimination does not interfere with the subsequent process, but can easily be removed by extracting the ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate solution with acid and washing the acid extract with an organic, water-immiscible solvent.

The novel process thus has the advantage of reducing the ethyl 3-dimethylamino-2-phenylpropionate content in the preparation of tilidine so greatly and in a simple, rapid and low-cost way in an early stage of workup that it no longer has interfering effects on the final product.

## Example

13.7 g (0.05 mol) of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate (mixture of cis and trans isomers) [ethyl 3-dimethylamino-2-phenylpropionate content (HPLC): 1%], dissolved in 40 ml of cyclohexane, was refluxed with 3.0 g (0.05 mol) of acetic acid for 2 hours. After cooling, 30 ml of water were added. The two-phase mixture was made alkaline with sodium hydroxide solution. The aqueous phase was then separated off. The organic phase was washed with 30 ml of water and concentrated. 13.4 g (98%) of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate isomer mixture of unchanged composition in respect of the cis/trans ratio were obtained with an ethyl 3-dimethylamino-2-phenylpropionate content of 0.05% (HPLC).

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We claim:

- A process for reducing the content of ethyl  
5 3-dimethylamino-2-phenylpropionate in a solution, contaminated  
therewith, of ethyl  
2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in a  
water-immiscible solvent, which comprises adding from 0.5 to 2.0  
equivalents of a carboxylic acid per mole of ethyl  
10 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate to this  
solution, and stirring this mixture at a temperature of from 50°C  
to 100°C.

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PCT

WELTORGANISATION FÜR GEISTIGES EIGENTUM  
Internationales Büro



INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE  
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation <sup>7</sup> :

C07C 227/40

A1

(11) Internationale Veröffentlichungsnummer: WO 00/43353

(43) Internationales

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(30) Prioritätsdaten:

199 02 590.8

22. Januar 1999 (22.01.99)

DE

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wigshafen (DE).

(72) Erfinder; und

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(81) Bestimmungsstaaten: AE, AL, AM, AT, AU, AZ, BA, BB,  
BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE,  
ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,  
KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,  
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,  
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,  
US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE,  
LS, MW, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent  
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches  
Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR,  
IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF,  
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht

Mit internationalem Recherchenbericht.

(54) Title: METHOD FOR REDUCING 3-DIMETHYLAMINO-2-PHENYLPROPION-ACID ETHYL ESTER-CONTENT IN SOLU-  
TIONS OF 2-DIMETHYLAMINO-1-PHENYL-3-CYCLOHEXENE-1-CARBOXYLIC ACID ETHYL ESTER

(54) Bezeichnung: VERFAHREN ZUR REDUKTION DES 3-DIMETHYLAMINO-2-PHENYLPROPIONSÄURE-  
ETHYLESTER-GEHALTS IN LÖSUNGEN VON 2-DIMETHYLAMINO -1-PHENYL -3- CYCLO-  
HEXEN-1-CARBONSÄUREETHYLESTER

(57) Abstract

The invention relates to a method for reducing the content of 3-dimethylamino-2-phenylpropionic acid ethyl ester in a solution that is contaminated therewith, whereby the solution is 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylic acid ethyl ester, in a solvent which cannot be mixed with water. According to the invention, 0.5 to 2.0 equivalents of a carboxylic acid per mol 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylic acid ethyl ester is added to the solution and this mixture is stirred at a temperature of 50 °C to 100 °C.

(57) Zusammenfassung

Es wird ein Verfahren zur Reduktion des Gehalts an 3-Dimethyl-amino-2-phenylpropionsäureethylester in einer hiermit verunreinigten Lösung von 2-Dimethylamino-1-phenyl-3-cyclohexen-1-carbonsäureethylester in einem mit Wasser nicht mischbaren Lösungsmittel beschrieben, welches darin besteht, dass man diese Lösung mit 0,5 bis 2,0 Äquivalenten einer Carbonsäure pro Mol 2-Dimethylamino-1-phenyl-3-cyclohexen-1-carbonsäureethylester versetzt und dieses Gemisch bei einer Temperatur von 50°C bis 100°C rührt.



## DECLARATION AND POWER OF ATTORNEY

As a below named inventors, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

A PROCESS FOR REDUCING THE CONTENT OF ETHYL 3-DIMETHYLAMINO-2-PHENYLPROPIONATE IN SOLUTIONS OF ETHYL 2-DIMETHYLAMINO-1-PHENYL-3-CYCLOHEXENE-1-CARBOXYLATE

the specification of which:

☐ is attached hereto.

☒ was filed on July 17, 2001 as  
Application Serial No. 09/889,383  
and was amended on \_\_\_\_\_.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

☐ In compliance with this duty, attached is an information disclosure statement.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
			Yes	No
<u>199 02 590.6</u>	<u>Germany</u>	<u>1/22/99</u>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>
_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>
_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>
Number	Country	Date Filed		

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is

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not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

<u>PCT/EP 00/00306</u>	<u>January 15, 2000</u>	<u>Published</u>
Serial No.	Date	Status

I hereby appoint KEIL & WEINKAUF their attorneys and/or agents: Herbert B. Keil, Reg. No. 18,967; Russell E. Weinkauff, Reg. No. 18,495; Gerald H. Bjorge, Reg. No. 32,386; Norman G. Torchin, Reg. No. 34,068; Malcolm J. MacDonald, Reg. No. 40,250; Henry R. Jiles, Reg. No. 32,677; Jason D. Voight, Reg. No. 42,205; George F. Helfrich, Reg. No. 22,350; Ronald H. Smith, Reg. No. 43,679 the address of all being KEIL & WEINKAUF, 1101 Connecticut Avenue, N.W., Suite 620, Washington, D.C. 20036 (telephone (202)659-0100), with full power to prosecute this application and transact all business in the Patent Office connected therewith.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Marco THYES

Full name of sole or first inventor

Marco Thyes  
Inventor's signature

28.09.01  
Date

Germany  
Residence

German  
Citizenship

Mendelsohnstrasse 31, 67061 Ludwigshafen, Germany

Post Office Address

\*\*\*\*\*

Wolfgang FALKENBERG

Full name of second joint inventor, if any

Wolfgang Falkenberg  
Inventor's signature

16.10.01  
Date

Germany  
Residence

German  
Citizenship

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1 2 3 4 5 6 7 8 9 0

300

<u>Ulrich SCHNEIDER</u>	
Full name of third joint inventor	
<u>U. Schneider</u>	<u>28.9.01</u>
Inventor's signature	Date
<u>Germany DEX</u>	<u>German</u>
Residence	Citizenship

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Post Office Address  
\*\*\*\*\*



09889383 020502  
DT05 Rec'd PCT/PTO 07 OCT 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of  
THYES et al.

Serial No. 09/889,383

Filed: July 17, 2001

For: A PROCESS FOR REDUCING THE CONTENT OF ETHYL  
3-DIMETHYLAMINE-2-PHENYL-PROPIONATE IN SOLUTIONS OF ETHYL 2-  
DIMETHYLAMINE-1-PHENYL-3-CYCLOHEXENE-1-CARBOXYLATE

I hereby certify that this correspondence is being deposited with the  
United States Postal Service as first class mail in an envelope  
addressed to: Commissioner of Patents and Trademarks,  
Washington, D.C. 20231, on:

October 3, 2002

Date of Deposit

KAREN STAMPER

Person Making Deposit

Signature

October 3, 2002

Date of Signature

Honorable Comm'r. of Patents  
Washington, D.C. 20231

CHANGE OF CORRESPONDENCE ADDRESS/  
ASSOCIATION WITH CUSTOMER NUMBER REQUEST

Sir:

The office of the attorney of record in this application has moved to the following  
new address:

**Keil & Weinkauff**  
**1350 Connecticut Ave., N.W.**  
**Washington, D.C. 20036**  
**(202) 659-0100**

It is further requested that this application be associated with Customer No.  
26474 as shown below:



Respectfully submitted,  
KEIL & WEINKAUF

*HBK*  
Herbert B. Keil  
Reg. No. 18,967

HBK/kas

1350 Connecticut Ave., N.W.  
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(202)659-0100